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Evaluation of vitamin D levels in pregnant women with familial mediterranean fever (FMF)

Vitamin D in familial mediterranean fever

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Abstract
Aim: There is an essential role of D vitamin in the fetal birth weight and bone development of the fetus. The main goal of this paper is to compare the vitamin D levels of pregnant women with familial Mediterranean fever (FMF) and normal pregnant women.
Material and Methods: Medical records of pregnant women (n=46) diagnosed with FMF and control group pregnants (n =31) were evaluated retrospectively.
Results: The vitamin D levels of pregnant women with FMF and normal healthy pregnants were 11.59 ± 6.7 ng/mL and 17.42 ± 9.36 ng/mL, respectively (p = 0,002). The birth weight of fetuses in the control group was significantly higher than the average birth weight of pregnant women with FMF (p = 0,022). Besides, a statistical difference was detected between two groups for vitamin D levels
Discussion: Pregnancies complicated by FMF could have additional morbidities. The presence of FMF in pregnancy may change the course of the pregnancy. These pregnant women have low levels of vitamin D. Pregnant women with FMF could have low fetal birth weight. Low vitamin D levels may cause this situation in the pregnancy.

Keywords
Vitamin D, Familial mediterranean fever, Pregnancy, Fetal birth weight, FMF

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Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory condition represented by recurrent polyserositis attacks and fever. The most accused causes are the mutations of the MEFV (Mediterranean Fever) gene, located on the q (small region of the chromosome) region of the 16th chromosome. The most devastating complication of FMF is amyloidosis, which could lead to chronic renal failure and, eventually, mortality. Besides, it may also affect other organs and tissues. Adults in the fertility period are also affected by the disease. Drug usage in this condition can be useful for the reproductive system and pregnancy period. Colchicine is the leading medical medication of choice for FMF. It is usually used to prevent and reduce the intensity of FMF exacerbations and the progress of amyloidosis. Colchicine usage in pregnant women and breastfeeding is known to be safe. The usage of colchicine has been reported to have positive effects on the frequency of fertility and pregnancy losses. Colchicine is the only effective drug, but there is still an unclarified issue regarding that there is a 30% responsiveness to the treatment with the colchicine in the FMF [1-4].

Vitamin D is structurally in the form of steroid hormones that has an essential role in the functioning of the musculoskeletal system, bone health, and human metabolism. Homeostasis of calcium and phosphorus is dependent on vitamin D. Vitamin D has immunomodulatory and pleiotropic effects. Vitamin D intake from diet has beneficial effects according to several in vivo studies conducted on laboratory animal models such as SLE, Crohn disease / ulcerative colitis, and collagen- induced arthritis. Circulating levels of vitamin D are decreased in several inflammatory conditions, according to reports of the previous studies. In cases such as cancer, muscle weakness, insulin resistance, diabetes, cardiovascular diseases, tuberculosis, and in the fight against chronic diseases, it should be carefully evaluated [5-8].

Although there are publications on the role of vitamin D and pregnancy outcomes and related conditions, the importance of vitamin D levels in pregnant women with FMF has not been evaluated to date. The purpose of this paper is to assess vitamin D levels in pregnant women with FMF.

Material and Methods

The medical records of the perinatology department at a university hospital were reviewed. Forty-eight pregnant women with FMF and 31 pregnant women with no previous disease history were enrolled in the study. Two pregnant women were excluded from the study because one of them had multiple pregnancies, and the other had D&C with own request. The diagnosis of FMF was made according to the Tel-Hashomer criteria [9]. All procedures in the study were in accordance with the latest version of the Helsinki Declaration. Besides this, institutional guidelines were also considered. The hospital's local ethics committee approved the protocol and procedures of this study (09/14-10).

The amount of colchicine therapy in patients was 1–1.5 mg/day, and there was no information on patients who were taking any other drugs that could affect vitamin D levels. Pregnants in both groups had no bone diseases and a history of another drug usage. We collected all blood samples from all pregnants in a similar season to avoid the seasonal change of the sun on D vitamin status. We used 25 (OH) D levels to evaluate the D vitamin status of the pregnants.

The statistical package for the social sciences (SPSS) version 20.0 for Windows was used for all statistical analyses. An independent-samples t-test was performed when the normality results were met. We used the Mann-Whitney U test to compare continuous variables. When the assumptions of the Independent t-test were not met, Mann–Whitney U tests were performed to examine the other dependent variables between patient and healthy participants. P-value <0.05 was considered statistically significant. A chi-square test was performed for independence to compare two variables in a contingency table to see if they are related.

Results

The mean age of pregnant women with FMF and the control group was 27. 35 ± 5.95 and 29.32 ± 5.90, respectively (Table 1). The mean gravida number of FMF group and control group was 2.22 ± 1.30 and 1.97 ± 1,33, respectively. The mean parity number of cases of FMF and control group was 0.72 ± 0,81 and 0.55 ± 0,81, respectively. The mean fetal birth week of cases of FMF and control group was 38.04 ± 2.56 and 38.42 ± 1,23, respectively. Basal proteinuria levels were 146 ± 108.89 mg/dl and 156.52 ± 110.71, in the FMF group and control group, respectively. Birth weight was 2970 ± 670 gr in the FMF group and 3290 ± 310 gr in the control group. There was a statistically significant difference between the two groups in terms of birth weight (p: 0.022) (Table 2).

Table 1. Comparison of the age of healthy and patients

Variable	M	SD	t	df	p
Age			1,43	75	0,156
Healthy (n=31)	29,32	5,90			
Patient (n=46)	27,35	5,95			

Table 2. Comparison of healthy and patients by birth weight, gravida, Parity, basal proteinuria, birth week (n = 31 healthy and 46 patients)

Variable	M	SD	Mean Rank	U	z	p
Birth weight				492,50	-2,29	0,022
Healthy	3,29	0,31	46,11			
Patient	2,97	0,67	34,21			
Gravida				622,50	-1,00	0,318
Healthy	1,97	1,33	36,08			
Patient	2,22	1,30	40,97			
Parity				619,00	-1,08	0,280
Healthy	0,55	0,81	35,97			
Patient	0,72	0,81	41,04			
Basal proteinuria				651,50	-0,64	0,523
Healthy	156,52	110,71	40,98			
Patient	146,00	108,89	37,66			
Birth week				691,00	-0,24	0,812
Healthy	38,42	1,23	38,29			
Patient	38,04	2,56	39,48			

Healthy and patient participants were not significantly different in terms of the delivery method. Likewise, healthy and patient participants were not considerably different for body mass index (Table 3). Healthy participants were significantly different from participants with FMF for the level of vitamin D (p =0,002). The concentration of vitamin D in pregnant women with FMF was considerably lower than the healthy participants. Vitamin D levels were 17.42 ± 9.36 ng/mL and 11.59 ± 6.70 ng/mL in control group and FMF group, respectively. However, the healthy participants did not differ significantly from patient participants in terms of the levels of albumin and total protein. Albumin levels were 3.70 ± 0.45 g/dL and 3.64 ± 0.47 g/dL in healthy pregnants and FMF group, respectively. Total protein levels were 6.74 ± 0.37 g/dL and 6.62 ± 0.59 g/dL in healthy pregnants and FMF group, respectively.

Table 3. Comparison of healthy and patients by age, birth weight, gravida, parity, bazal proteinuria, birth week, delivery method, body mass index (n = 31 healthy and 46 patients)

	Healthy n (%)	Patient n (%)	x^2	df	p
Delivery method			1,38	1	0,240
Vaginal delivery	10 (32,3)	21 (45,7)			
Caesarean section	21 (67,7)	25 (54,3)			
Body Mass Index			5,15		0,248
Normal weight	8 (25,8)	11 (23,9)			
Pre-obesity	14 (45,2)	26 (56,5)			
Obesity class I	6 (19,4)	8 (17,4)			
Obesity class II	3 (9,7)	0 (0)			
Obesity class III	0 (0)	1 (2,2)			

Discussion

We showed that maternal serum concentrations of vitamin D are decreased in pregnant women diagnosed with FMF compared to pregnant women in the control group. Some studies have investigated the vitamin D levels in adult patients with FMF in the literature, but this is the first study, to our knowledge, that evaluates the D vitamin concentrations in pregnant women diagnosed with FMF [10].

Vitamin D deficiency is beginning to be considered a public health problem. Reduced vitamin D levels in pregnant women have been associated with poor pregnancy outcomes. Low levels of maternal vitamin D during pregnancy period have been reported to be associated with several poor newborn outcomes. These adverse outcomes include a detrimental effect on fetal bone and teeth health, intrauterine growth retardation (IUGR), preterm birth, hypertensive disorders in pregnancy, and risk of infectious conditions. Previous studies have shown different associations between maternal vitamin D status and fetal growth. Interestingly, there is some knowledge regarding the irrelevance between maternal vitamin D levels and neonatal anthropometric measures. According to some publications, neonatal outcomes are not affected by maternal vitamin D status [11-13].

Low birth weight is a leading neonatal problem and causes future morbidities. Babies with low birth weight have high risk medical problems and inguinal canal pathologies, NEC, severe respiratory problems requiring interventions. They are also candidates for surgical problems such as premature retinopathy, patent ductus arteriosus, ventriculomegaly. The causes of low birth weight could be listed as fetal, maternal, and placental. It is essential to provide proper diet and nutritional care of mothers during pregnancy [14].

It is known that the level of maternal vitamin D affects the immunity, bone development, and birth weight of the fetus. There is no consensus regarding the duration of vitamin D supplementation during pregnancy and the way of administration because of the heterogeneity of the trials of vitamin D supplementation in the pregnancy. Currently, available evidence suggests that vitamin D supplement during gravidity decreases the risk of preterm delivery, intrauterine growth retardation, teeth health of the fetus, and infectious conditions of a newborn like respiratory infections and sepsis. However, new good-designed, more extensive clinical trials are needed. The usage of low-dose vitamin D during pregnancy is considered safe for now. From the perspective of neonatal health, there is still no definitive conclusion regarding the potential long-term adverse reactions of adding vitamin D to the diet. Therefore, many randomized clinical trials are needed to monitor fetal health in pregnant women supplemented with vitamin D during pregnancy. Our study shows that decreased maternal vitamin D levels may have harmful effects on fetal birth weight in pregnant women with FMF disease [15-17].

In a trial evaluating 46 pregnant women with FMF, preterm labor rupture and cesarean frequency were increased, but preterm delivery, gestational diabetes, and preeclampsia frequency did not differ. Colchicine usage has been reported to be safe, and it reduces the abortion rate in pregnancy, according to a study conducted by Yasar et al. [18]. The preterm birth rate did not differ in the groups in our research, concordant with previously reported studies.

Limitations

The lack of PTH and calcium levels and neonatal outcomes could be listed as limitations of our study.

Conclusion

Maternal vitamin D levels have an essential role in the fetal birth weight and bone development of the fetus. Besides, it has a role in the event of fetal immunity. However, it is difficult to make conclusions about the optimal D vitamin levels required during pregnancy. Specific findings cannot be made in the usage of D vitamin during the pregnancy due to the following factors: heterogeneity of studies on this issue, the length of the duration of hypovitaminosis due to vitamin D deficiency, and other potential confusion. In light of the available data, vitamin D supplement during pregnancy reduces the incidence of preterm birth, the risk of miscarriage, low fetal birth weight, tooth decay in infants, newborn infectious diseases such as respiratory infections, and sepsis rates. These conditions are inversely proportional to the level of vitamin D. However, there is a need for well-designed, large RCTs with many participants. The safety of D vitamin during pregnancy is acceptable. The usage of low-dose vitamin D during pregnancy seems to be safe in the short term for now. What side effects vitamin D supplements will cause in gestation for a long time is based upon the research investigating the impact of neonatal health.

Colchicine treatment seems to be safe in pregnant women with FMF. The vitamin D levels are decreased in pregnant women with FMF, and this clinical situation may be responsible for poor obstetric outcomes in these pregnant population. Pregnants with FMF should be encouraged to take D vitamin supplementation during pregnancy.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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